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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,280	05/27/2005	Jane Sanders	AATLP-001	1845

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EXAMINER	
WOODWARD, CHERIE MICHELLE	
ART UNIT	PAPER NUMBER
1647	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,280	SANDERS ET AL.	
	Examiner	Art Unit	
	CHERIE M. WOODWARD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *121,122,125-139,141-143 and 145-197* is/are pending in the application.

4a) Of the above claim(s) *138,139,141-143 and 145-197* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *121, 122,125-133, 136,and 137* is/are rejected.

7)☒ Claim(s) *134 and 135* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/20/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, (claims 121-122, and 125-137), as drawn to SEQ I D NOs: 1 and 6, in the reply filed on 2/6/2008 is acknowledged. Claims 1-120. 123, 124, 140, and 144 have been cancelled by Applicant. Claims 138, 139, 141-143, and 145-197 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/6/2008.

It is noted that in the Response to the Restriction Requirement, filed 2/6/2008, Applicant only elected one SEQ ID NO: to be searched, SEQ ID NO: 1, in compliance with the requirement for restriction election under lack of unity. However, the examiner noted that Applicant had previously elected SEQ ID NOs: 1 and 6 in the Response filed 10/22/2007. Because SEQ ID NO: 1 is directed to a VH chain of an antibody and SEQ ID NO: 6 is drawn to a VL chain of an antibody, the examiner has rejoined SEQ ID NO: 6 so that the claims may be examined as they are drawn to both sequences (compare claims 134 and 135).

Formal Matters

2. The preliminary amendments to the specification and the drawing replacement sheets, filed 5/27/2005, are acknowledged and entered.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 7/20/2005 has been considered by the examiner. A signed copy is attached hereto.

Claim Rejections - 35 USC § 101, Product of Nature

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 121, 122, 125, 128, and 131 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims, as written, read on naturally occurring human autoantibodies that are reactive with the TSH receptor (claims 121 and 122) that inherently inhibit TSH binding to the TSH receptor (claims 125 and 131) and stimulate cAMP production by cells expressing the TSH receptor (claims 128 and 131). Human polyclonal sera can functionally act as

monoclonal preparations (see, for example, Saper et al., J Comp Neuro. 2003 Oct 13. 465:161-163, especially at p. 162, column 1, first full paragraph). Further, polyclonal sera are comprised of a multiplicity of monoclonal antibodies each directed to specific antigenic epitopes.

WO 91/09137 (published 27 June 1991, cited in Applicant's IDS of 7/20/2005) provides additional evidence that the instant claims read on naturally occurring human autoantibodies that are reactive with the TSH receptor. Example VIII discusses human autoantibodies in the serum of patients with autoimmune thyroid disease (pp. 101-113). Example VIII teaches human autoantibodies against the TSH receptor in Graves' disease and Hashimoto's thyroiditis (p. 101, lines 7-11). These autoantibodies are taught as capable of interacting with the TSH receptor and of either mimicking the action of TSH in leading to thyroid hyperfunction or of blocking TSH action with consequent hypothyroidism (p. 101, lines 11-15). The physical characteristics/properties of the autoantibodies include interacting with the TSHR (compare instant claims 121 and 122) and competing with TSH for binding to TSHR (compare instant claims 125 and 131), as well as stimulating TSHR antibodies that induce cAMP production in thyroid cells (compare instant claims 128 and 131). Example VIII also recites that both types of autoantibodies (competitive and stimulatory TSHR binding antibodies) may be present in the same patient (p. 101, lines 31-32).

In order to overcome this rejection, Applicant should amend the claims to recite that the antibodies are isolated and/or purified.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 121, 122, 125, 128, and 131 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 91/09137 (published 27 June 1991, cited in Applicant's IDS of 7/20/2005).

The claims are drawn to a human monoclonal antibody, recombinant antibody, or a fragment thereof that is a binding partner for a TSH receptor and is reactive therewith, wherein the binding partner has a characteristic of patient serum TSH receptor autoantibodies; wherein the characteristic includes inhibition of TSH binding to the TSH receptor and with respect to stimulation of cAMP production by cells expressing the TSH receptor. The claims, as written, broadly read on naturally occurring human autoantibodies.

WO 91/09137 teaches binding partners for a TSH receptor comprising antibodies, including monoclonal antibodies (pages 36-42, especially p. 39). Example VIII teaches human autoantibodies in the serum of patients with autoimmune thyroid disease (pp. 101-113). Example VIII teaches human autoantibodies against the TSH receptor in Graves' disease and Hashimoto's thyroiditis (p. 101, lines 7-11). These human autoantibodies are taught as capable of interacting with the TSH receptor and of either mimicking the action of TSH in leading to thyroid hyperfunction or of blocking TSH action with consequent hypothyroidism (p. 101, lines 11-15). The physical characteristics/properties of the autoantibodies include interacting with the TSHR (compare instant claims 121 and 122) and competing with TSH for binding to TSHR (compare instant claims 125 and 131), as well as stimulating TSHR antibodies that induce cAMP production in thyroid cells (compare instant claims 128 and 131). Example VIII also recites that both types of autoantibodies (competitive and stimulatory TSHR binding antibodies) may be present in the same patient (p. 101, lines 31-32).

The polyclonal antibodies found in human serum are comprised of a multiplicity of monoclonal antibodies each directed to a specific antigenic epitope. Human polyclonal sera can functionally act as monoclonal preparations.

8. Claims 121, 122, and 128 are rejected under 35 U.S.C. 102(b) as being anticipated by Akamizu et al., (Endocrinology. 1999 Apr;140(4):1594-1601).

The claims recite as stated above. Akamizu et al., teach isolated and reconstituted the Ig genes of two B cell clones (101–2 and B6B7) producing a monoclonal thyroid-stimulating antibody (TSAb), a stimulating type of TSHRAb, obtained from human patients with Graves' disease (abstract) (compare instant claims 121 and 122). The activity of the human monoclonal antibodies to elevate cAMP levels in cells expressing TSHR is taught in Figures 3 and 4 (compare instant claim 128).

9. Claims 121, 122, 125-133 are rejected under 35 U.S.C. 102(b) as being anticipated by Kohn et al., (J Clin Endo and Metab. 1997;82(12):3998-4009).

The claims recite as stated above. Kohn et al., teach monoclonal THSR antibodies that have been subcloned into heterohybridomas produced from the lymphocytes of a patient who has Hashimoto's thyroiditis (abstract; p. 3999, materials and methods) (compare instant claims 121 and 122). Twelve clones produced stimulating TSHR antibodies that increased cAMP levels in cells expressing TSHR (abstract; Figure 1; p. 3999, column 2, last paragraph to p. 4000, column 1, first paragraph; p. 4000, column 2, fourth paragraph) (compare instant claims 121, 122, 128, and 131). The clones are taught as being weak inhibitors of TSH binding in assays measuring TSH binding-inhibiting IgGs (TBIIs)

(abstract) (compare instant claims 125 and 131). Kohn et al., teaches that stimulating TSHR antibodies (TSHRAbs) differ from TSHR antibodies (TBIIs) that inhibit TSH binding or block TSH activity (p. 3998, column 2, last paragraph) (compare instant claim 131).

Kohn et al., teach the ability of normal controls (IgG), sera from patients with Graves' (IgG) and the antibodies from the cloned heterohybridomas, to increase cAMP levels in cells expressing TSHR (Table 1, p. 4002; Figure 2, p. 4003) (compare instant claims 129, 130, and 133). Kohn et al., teach the ability of normal human IgG or the clonal stimulating TSHRAbs to bind to human thyroid membranes in the presence of TSH, LH, or hGC (i.e. competitive binding assay) (Table 2, p. 4004; Figure 3, p. 4004) (compare instant claims 126, 127, and 132). Percent inhibition is also shown in a commercial TRAK assay in Table 3 (p. 4005) and Figure 4 (compare instant claims 126, 127, and 132). Table 4 (p. 4006) teaches the ability of the clones that have TBII activity to inhibit TSH or Graves' IgG-increased cAMP activity (see also Figure 5, p. 4006) (compare instant claims 121,122, and 125-133).

With regard to inhibitory activity levels of claims 126, 127, 129, 130, 132, and 133, the claims use a measure of NIBSC international standard units, which are defined in the specification on page 58 as having 0.1 international unit per ampoule. However, this definition discloses concentration, but does not provide adequate information from which to compare activity levels (whether inhibitory or stimulatory) in the art, for example in concentrations of picomoles/μg or μg/ml, without experimental wet lab testing of the antibodies of the art against the NIBSC 90/672 international standard. Also compare Tables 1-3, 5-7, 9-11, and 14-19 on pp. 78-81, 83-86, 88-91, and 95-102 of the instant specification. Absent evidence to the contrary, the human anti-TSHR monoclonal antibodies taught by Kohn et al., meet the limitations of the claims for the requisite comparative NIBSC units of activity. Because the Patent Office does not have the facilities to comparatively test the human anti-TSHR monoclonal antibodies taught by the art for the requisite comparative NIBSC units of activity, the burden is on the application to show a novel and unobvious difference between the claimed TSHR binding partners and that of the prior art. See In re Brown, 59 CCPA 1036, 459 F.2d. 531, 173 USPQ 685 (CCPA 1972) (holding at 1041, "[a]s a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith") and Ex parte Gray, 10 USPQ 2d 1922, 1924-25 (PTO Bd. Pat. App. & Int.).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 136 and 137 are rejected in addition to claims 121, 122, 125-133 under 35 U.S.C. 103(a) as being unpatentable over Van Der Heijden et al., (Clin Exp Immunol. 1999;118:205-212) and Kohn et al., (J Clin Endo and Metab. 1997;82(12):3998-4009), as evidenced by WO 91/09137 (published 27 June 1991, cited in Applicant's IDS of 7/20/2005), UniProt, Accession No. P16473 (sequence version 1, 1 August 1990), and generally evidenced by Harlow et al., Eds. (Antibodies, A Laboratory Manual. Cold Spring Harbor Press. 1988).

The Examiner finds the following facts:

a. The claims recite as set forth above.

b. Van Der Heijden et al., teach fragments of human monoclonal phage antibodies (moPhabs) generated by phage display reactive with the TSH receptor (abstract). Cloning and expression of modified human scFv proteins is taught at p. 207, column 1, paragraph 3 (see also p. 208, column 1, first full paragraph). Expression and purification of scFv fragments are taught at p. 207, column 1, last paragraph. Binding of the moPhabs to the TSHR ectodomain is taught at

Figure 1, p. 209. Monovalent and bivalent scFv fragments were tested in a cAMP assay for their modulating effect on TSH-R function (p. 209, column 2, last paragraph) (compare instant claims 136 and 137).

c. Van Der Heijden et al., do not teach a fragment that has an inhibitory activity with respect to TSH binding to the TSH receptor or that has stimulatory activity with response to cAMP production (see page 210, column 1, first paragraph).

d. Kohn et al., teach human monoclonal THSR antibodies that have been subcloned into heterohybridomas produced from the lymphocytes of a patient who has Hashimoto's thyroiditis (abstract; p. 3999, materials and methods) (compare instant claims 121 and 122). Twelve clones produced stimulating TSHR antibodies that increased cAMP levels in cells expressing TSHR (abstract; Figure 1; p. 3999, column 2, last paragraph to p. 4000, column 1, first paragraph; p. 4000, column 2, fourth paragraph) (compare instant claims 121, 122, 128, and 131). The clones are taught as being weak inhibitors of TSH binding in assays measuring TSH binding-inhibiting IgGs (TBIIs) (abstract) (compare instant claims 125 and 131). Kohn et al., teaches that stimulating TSHR antibodies (TSHRAbs) differ from TSHR antibodies (TBIIs) that inhibit TSH binding or block TSH activity (p. 3998, column 2, last paragraph) (compare instant claim 131). Kohn et al., also teach the ability of normal controls (IgG), sera from patients with Graves' (IgG) and the antibodies from the cloned heterohybridomas, to increase cAMP levels in cells expressing TSHR (Table 1, p. 4002; Figure 2, p. 4003) (compare instant claims 129, 130, and 133). Kohn et al., teach the ability of normal human IgG or the clonal stimulating TSHRAbs to bind to human thyroid membranes in the presence of TSH, LH, or hGC (i.e. competitive binding assay) (Table 2, p. 4004; Figure 3, p. 4004) (compare instant claims 126, 127, and 132). Percent inhibition is also shown in a commercial TRAK assay in Table 3 (p. 4005) and Figure 4 (compare instant claims 126, 127, and 132). Table 4 (p. 4006) teaches the ability of the clones that have TBII activity to inhibit TSH or Graves' IgG-increased cAMP activity (see also Figure 5, p. 4006) (compare instant claims 121,122, and 125-133).

e. The level of skill of those in the art encompasses skills in the field of molecular biology relating to the construction or generation of human monoclonal or recombinant antibodies or fragments thereof by standard and routine methodologies.

f. A person of ordinary skill in the art at the time the invention was made would have reasonably known that fragments of human monoclonal antibodies or human recombinant antibodies could be made against a known antigen or antigenic sequence, such as the TSHR.

g. Further, a person of ordinary skill in the art would have been able to make fragments of human monoclonal antibodies or human recombinant antibodies merely by using well-known methodologies and protocols, such as the ones taught by the Van Der Heijden et al., or Kohn et al., and the resulting structure and function of the constructs would have reasonably been predictable.

h. There was a recognized need in the art at the time the invention was made to find human antibodies that can be practically and cost-effectively used as diagnostics and as immunotherapetuics for thyroid-based autoimmune disorders such as Graves' disease and Hashimoto's thyroiditis (as evidenced by WO 91/09137, p. 3, line 25-33, p. 4, lines 31-34, and p. 5, lines 26-34).

i. At the time of the instant invention, there were a finite number of identified predictable potential solutions recognized in the art to solve the problem making find human antibodies that can be practically and cost-effectively used as diagnostics and as immunotherapetuics for thyroid-based autoimmune disorders such as Graves' disease and Hashimoto's thyroiditis.

j. One of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success to generate human monoclonal antibodies, human recombinant antibodies or fragments of human monoclonal antibodies with a reasonable expectation of success because the art teaches the generation of these antibodies with varying degrees of functional activities.

k. A person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance, the fact that a combination was obvious to try might show that it was obvious under 35 USC 103 (see KSR v. Teleflex, 550 US ___, 82 USPQ2d 1385, 1397 (S.Ct. 2007).

l. The production of monoclonal antibodies via hybridomas, or through recombinant techniques, including fragments thereof is has been routine in the art since at least 1988, as evidenced generally by Harlow et al., Eds. (Antibodies, A Laboratory Manual. Cold Spring Harbor Press. 1988).

m. The amino acid sequence of human TSHR was well known in the art at the time of the instant invention, as evidenced by UniProt, Accession No. P16473(sequence version 1, 1 August 1990).

In view of the facts recited above, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the prior art elements according to known methods to yield predictable results or alternatively it would have been obvious to try given the teachings of the prior art. Van Der Heijden et al., teach fragments of human monoclonal phage antibodies (moPhabs) generated by phage display reactive with the TSH receptor (abstract). Cloning and expression of modified human scFv proteins is taught at p. 207, column 1, paragraph 3 (see also p. 208, column 1, first full paragraph). Expression and purification of scFv fragments are taught at p. 207, column 1, last paragraph. Binding of the moPhabs to the TSHR ectodomain is taught at Figure 1, p. 209. Monovalent and bivalent scFv fragments were tested in a cAMP assay for their modulating effect on TSH-R function (p. 209, column 2, last paragraph) (compare instant claims 136 and 137). However, Van Der Heijden et al., do not teach a fragment that has an inhibitory activity with respect to TSH binding to the TSH receptor or that has stimulatory activity with response to cAMP production (see page 210, column 1, first paragraph).

Kohn et al., teach human monoclonal THSR antibodies that have been subcloned into heterohybridomas produced from the lymphocytes of a patient who has Hashimoto's thyroiditis. A person of ordinary skill in the art could have easily used a protease to cleave the Fc region off of the clones generated by Kohn et al., to create a fragment or alternatively, could have generated moPhabs using the methodologies taught by Van Der Heijden, that would bind the same or closely related epitopes of the monoclonal clones taught by Kohn et al., thus predictably preserving functional activity due to antibody-antigen interaction with specific regions of the TSHR (compare instant claims 136 and 137). Creating fragments from whole antibodies through proteolytic cleavage is old and routine in the art. Cleavage of the Fc region, leaving only the Fab region, would not adversely affect the activity of the fragments of the antibodies taught by Kohn et al.

The person of ordinary skill in the art could have combined the teachings of the art to create human monoclonal antibodies, recombinant antibodies, and fragments thereof, as claimed, by known methods to produce active binding partners to TSHR (compare instant claims 136 and 137). The production of monoclonal antibodies via hybridomas, or through recombinant techniques, including the production of antibody fragments is has been routine in the art since at least 1988 (see generally, Harlow et al., Eds.). One of skill in the art would have recognized that the results of the combination of functional, active human monoclonal or recombinant antibodies or fragments thereof would be useful in a commercial and clinical setting and would have been motivated at least to try to produce human monoclonal antibodies, recombinant antibodies, and/or fragments thereof with the requisite activity levels in order to treat and/or diagnose thyroid-based autoimmune disease. It is old and well known in the art

that different antibody clones can have different activity levels depending on the epitope to which they bind. Recombinant TSHR was known in the art (as evidenced by WO 91/09137). The skilled artisan could have reasonably and predictably used the recombinant TSHR to map the autoantibody TSHR epitopes and to find competitive or antagonistic antibodies thereto for use in diagnostics or therapeutics. Further, it would have been obvious to create an active functional human monoclonal antibody to compete with the autoantibodies from patients' sera for use in diagnostic competition assays. The known need in the art would have been sufficient to provide the motivation and rationale to try (as evidenced by WO 91/09137).

One of skill in the art would also have had a reasonable expectation of success because a recombinant TSHR was known in the art (as evidenced by WO 91/09137), the sequence of TSHR was known in the art (as evidenced by UniProt, Accession No. P16473, sequence version 1, 1 August 1990), and methods of making human monoclonal and recombinant antibodies and fragments thereof were old and routine in the art (as evidenced by Harlow et al., Eds). Thus, the generation of a human monoclonal antibody, a recombinant human antibody, or fragments thereof, directed to and reactive with the TSHR wherein the antibody retains the requisite functional characteristics and activity levels to be of use in commercial and clinical applications, would have yielded nothing more than predictable results to one of ordinary skill in the art at the time the invention was made. This is demonstrated by the fact that Kohn et al., made human monoclonals from heterohybridomas with the requisite activity levels, and Van Der Heijden made scFv fragments using phage display techniques.

As stated above, and absent evidence to the contrary, the human anti-TSHR monoclonal antibodies taught by Kohn et al., meet the limitations of the claims for the requisite comparative NIBSC units of activity (compare Tables 1-3, 5-7, 9-11, and 14-19 on pp. 78-81, 83-86, 88-91, and 95-102 of the instant specification). Because the Patent Office does not have the facilities to comparatively test the human anti-TSHR monoclonal antibodies taught by the art for the requisite comparative NIBSC units of activity, the burden is on the application to show a novel and unobvious difference between the claimed TSHR binding partners and that of the prior art. See In re Brown, 59 CCPA 1036, 459 F.2d. 531, 173 USPQ 685 (CCPA 1972) (holding at 1041, "[a]s a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith") and Ex parte Gray, 10 USPQ 2d 1922, 1924-25 (PTO Bd. Pat. App. & Int.).

Allowable Subject Matter

14. Claims 134 and 135 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. It is noted that claims 134 and 135 are **only examined** with respect to SEQ ID NOs: 1 and 6, as elected (see Election/Restriction paragraph, above). SEQ ID NOs: 1 and 6 are free of the prior art.

Conclusion

Claims 121, 122, 125-133, and 136-137 are rejected.
Claims 134 and 135 are objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHERIE M. WOODWARD whose telephone number is (571)272-3329. The examiner can normally be reached on Monday - Friday 9:00am-5:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cherie M. Woodward/
Examiner, Art Unit 1647